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Award Number:
W81XWH-07-1-0032

TITLE:
Vaccine Immunotherapy for Prostate Cancer

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REPORT DATE:
May 2009

TYPE OF REPORT:
Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

X Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
01-05-2009	Annual	15 April 2008-14 April 2009

4. TITLE AND SUBTITLE
Vaccine Immunotherapy for Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-07-1-0032

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
David M. Lubaroff, PhD

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Iowa
Iowa City, IA 52242

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research
and Materiel Command
Fort Detrick, MD 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The purpose of the research supported by this award is to conduct a Phase II clinical trial (study) of an adenovirus/PSA (Ad/PSA) vaccine for the treatment of prostate cancer. Two protocols have been used in the trial: #1 - *Phase II study of Adenovirus/PSA vaccine in men with recurrent prostate cancer after local therapy*; and #2 - *Phase II study of Adenovirus/PSA vaccine in men with hormone refractory prostate cancer*. In the first protocol men with newly recurrent prostate cancer were randomized to one of two arms of the study. Patients in Arm A received the Ad/PSA vaccine only; three injections spaced 30 days apart. Patients in Arm B received androgen deprivation therapy (ADT) followed at day 14 by the Ad/PSA vaccine, again with three injections. In the second protocol men with hormone refractory prostate cancer were injected with the vaccine only, three injections 30 days apart. The patients were followed for toxicity, the development of anti-PSA immune responses, and evidence of a clinical effect of the vaccination. The latter includes changes in serum PSA and prostatic acid phosphatase (PAP) levels and in the PSA doubling times (PSADT). Patients in protocol #2 also have CT and bone scans to monitor their prostate cancer.

15. SUBJECT TERMS
Prostate cancer; immunotherapy; vaccine

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	9	**19b. TELEPHONE NUMBER** *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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INTRODUCTION

The purpose of the research supported by this award is to conduct a Phase II clinical trial (Study) of an adenovirus/PSA (Ad/PSA) vaccine for the treatment of prostate cancer. Two protocols are being used in the trial: #1 – *Phase II study of adenovirus/PSA vaccine in men with recurrent prostate cancer after local therapy,* and #2 – *Phase II study of adenovirus/PSA vaccine in men with hormone refractory prostate cancer*. In the first protocol men with recent documentation of recurrent prostate cancer are randomized to one of two arms of the study. Patients in Arm A receive the Ad/PSA vaccine only; three injections spaced 30 days apart. Patients in Arm B will receive androgen deprivation therapy (ADT) followed at day 14 by the first of three Ad/PSA injections. In the second protocol men with hormone refractory prostate cancer are injected with the vaccine only, three injections 30 days apart. The patients are followed for toxicity, the development of anti-PSA immune responses, and evidence of a clinical effect of the vaccination. The latter includes changes in serum PSA and prostatic acid phosphatase (PAP), and the PSA doubling times (PSADT). Patients in protocol #2 also have CT and bone scans to monitor their prostate cancer.

BODY:

The first year of the award, from April 1, 2007 through March 31, 2008, was occupied by negotiations and submissions of documents to the DOD's PCRP, including the Human Subjects Research Review Board (HSRRB), the FDA, NIH's Recombinant DNA Review Committee (RAC), the University of Iowa IRB, the Iowa City VA Medical Center IRB, and the Iowa City VA Medical Center Research and Development Committee.

Recruitment – Patients were initially recruited into the trial from the Urology Clinic in the University of Iowa Hospitals and Clinics (UIHC) and the Urology Service at the adjacent Iowa City VA Medical Center. Additional recruitment was through (1) referrals from private practice physicians (urologists, medical oncologists, and radiation oncologists) following the mailing of a letter sent to these physicians in the State of Iowa and bordering regions of Nebraska, Missouri, Illinois, Minnesota, and Wisconsin; (2) the listing of the trial on www.clinicaltrials.gov; and (3) presentation of results from our successful Phase I trial of the Ad/PSA vaccine at the annual meeting of the American Urological Association (AUA) and the North Central Section of the AUA. In the first year we screened a total of 76 patients for their eligibility to enter the trial, but only 15 patients were enrolled (19.7%). Table 1 details the reasons for the screen failures.

We had planned for a larger accrual of patients into the trial and have taken several steps to enhance recruitment. Since these measures were initiated after the period covered by this Annual Report they will be documented in a separate Interim Report to be submitted to the CDMRP.

Table 1		
Screening Failures		
Protocol #1		
	Number	**Percent**
Candidate for radiation therapy	2	5.9%
Gleason score >7	6	17.6%
Double time< 6 mo	1	2.9%
Pre-surgical PSA > 20	1	2.9%
CT +	2	5.9%
BS +	1	2.9%
Not recurrent (1° diagnosis)	5	14.7%
PSA < .2	2	5.9%
PSA decreased	1	2.9%
Insurance refuses	1	2.9%
Seminal vesicle	1	2.9%
Hormone therapy	2	5.9%
No confirmed prostate cancer	1	2.9%
Refuses randomization	1	2.9%
Unknown – someone else called	1	2.9%
Not interested	1	2.9%
Sent information, no return call	4	11.8%
Protocol #2		
Bulky tumor	3	6.7%
+ CT with PSA>5	4	8.9%
+BS, doubling time < 12 mo	4	8.9%
+BS, PSA>5	14	31.1%
2nd malignancy	2	4.4%
PSA decreased	2	4.4%
On hormones but not refractory	3	6.7%
Chemo	3	6.7%
Behavior	2	4.4%
Not interested	1	2.2%
Sent information, no return call	7	15.6%

Enrollment - After all approvals were obtained the first patient enrolled was injected on April 8, 2008. In the period between April 8 2008 and the end of the first year, March 31, 2009 we enrolled 15 patients, 5 in protocol #1 (2 in Arm A and 3 in Arm B) and 10 in protocol #2. Table 2 provides data for the enrolled patients.

Table 2
Patients Enrolled from April 1, 2008 to March 31, 2009

Patient ID	Protocol	Arm	Information
APIIAHN-01	1	A	Received all 3 vaccinations and completed visits to 9 months.
APIIAHN-02	1	A	Received all 3 vaccinations and completed visits to 6 months.
APIIAADT-01	1	B	Received all 3 vaccinations and completed visits to 9 months.
APIIAADT-02	1	B	Received all 3 vaccinations and completed visits to 9 months.
APIIAADT-03	1	B	Received first 2 injections.
APIIB-01	2	---	Received all 3 injections and completed visits to 90 days; discontinued due to progressive disease.
APIIB-02	2	---	Received all 3 vaccinations and completed visits to 9 months.
APIIB-03	2	---	Vaccinations delayed due to falling serum PSA levels.
APIIB-04	2	---	Received all 3 vaccinations and completed visits to 9 months.
APIIB-05	2	---	Received all 3 vaccinations and completed visits to 6 months.
APIIB-06	2	---	Received all 3 vaccinations and completed visits to 6 months.
APIIB-07	2	---	Received all 3 vaccinations and completed visits to 90 days.
APIIB-08	2	---	Received all 3 vaccinations and completed visits to 90 days.
APIIB-09	2	---	Received all 3 vaccinations and completed visits to 90 days.
APIIB-10	2	---	Received first injection.

Adverse Events – During the period of report there were few vaccine-related adverse events (AE), all of them grade 1. Table 3 documents these vaccine-related AE.

Table 3
Vaccine-Related Adverse Events

Protocol #1; Arm A – Hormone Naïve Patients

Patient	Event	Grade	Vaccine Related
APIIAHN-01	Headache	1	Possible

No vaccine-related adverse events in the other Arm A patient. Total patients = 2

Protocol #1; Arm B – Androgen Deprivation Patients

No vaccine-related adverse events in any Arm B patients. Total patients = 3

Protocol #2; Hormone Refractory Patients

Patient	Event	Grade	Vaccine Related
APIIB-02	Headache	1	Possible
APIIB-06	Headache	1	Possible
	Flushing	1	Possible

No vaccine-related adverse events in any other Protocol 2 patients. Total patients = 10

Table 4 lists all of the adverse events documented for each of the currently enrolled patients whether they were deemed vaccine-related or not. The decisions on vaccine relatedness were made by the clinical team, consisting of the clinicians and our clinical trial coordinator.

Table 4
All Adverse Events

Protocol #1; Arm A – Hormone Naïve Patients

Patient	Event	Grade	Vaccine Related
APIIAHN-01	Headache	1	Possible
	Diarrhea	1	Unlikely
	Increase voiding frequency	1	Unlikely
	Facial flushing	2	Unlikely
APIIAHN-02	Diarrhea	1	unrelated

Protocol #1; Arm B – Androgen Deprivation Patients

Patient	Event	Grade	Vaccine Related
APIIAADT-01	Decreased libido	1	Unrelated
	Hot flashes	1	Unlikely
APIIAADT-02	Flushing	1	Unrelated
APIIAADT-03	None		
APIIAADT-04	None		

Protocol #2; Hormone Refractory Patients

Patient	Event	Grade	Vaccine Related
APIIB-01	Arthralgia	1	Unlikely
APIIB-02	Headache	1	Possible
	Back pain	1	Unrelated
	Hypertension	2	Unlikely
	Tension headache	1	Unlikely
	Anxiety	1	Unlikely
	Sore throat	1	Unlikely
APIIB-04	Dizziness	1	Unlikely
	Nasal congestion	1	Unlikely
	Hypertension	2	Unlikely
	Urinary tract infection	1	Unlikely
APIIB-05	Upper respiratory infection	2	Unlikely
	Common cold	1	Unlikely
APIIB-06	Headache	1	Possible
	Flushing	1	Possible
APIIB-07	Dizziness	1	Unlikely
	Headache	2	Unlikely
	Diarrhea	2	Unlikely
APIIB-08	None		
APIIB-09	None		
APIIB-10	None		

KEY RESEARCH ACCOMPLISHMENTS:

For each patient we collected serum for future measurements of anti-PSA and anti-adenovirus antibodies, isolated lymphocytes from the peripheral blood for the measurement of anti-PSA and anti-adenovirus T cell responses, and measured serum levels of PSA and PAP.

PSA Doubling Times (PSADT) – One of the measurements used to follow the clinical pattern of prostate cancer before and after therapy is the change in doubling time of the serum PSA levels. We have evaluated the PSADT of the two patients in protocol #1, Arm A and seven of the 9 patients in protocol #2. Since patients in protocol #1, Arm B are first treated with ADT we cannot follow their clinical progress. Table 5 demonstrates that of the nine patients, on whom we had sufficient data to calculate both pre-vaccination and post-vaccination PSADT values, six or 67%, had an increase and three or 33% had a decrease in the values.

Table 5
PSA Doubling Times (PSADT)

Patient	PSADT		Percent Change
	Pre-Vaccination	Post-Vaccination	
APIIAHN-01	26.7 months	20.9 months	-21.7%
APIIAHN-02	14.7 months	48.9 months	+232.7%
APIIB-01	7 months	3.8 months	-45.7%
APIIB-02	9.9 months	11 months	+11.1%
APIIB-04	6.3 months	15.8 months	+150.8%
APIIB-05	17.4 months	11.1 months	-36.2%
APIIB-06	3.1 months	6.1 months	+96.8%
APIIB-07	7.3 months	8.7 months	+19.2%
APIIB-08	5.2 months	10 months	+92.3%
Overall as of 6/25/09 – 6/9 patients (67%) demonstrated an increase in PSADT and 3/9 patients (33%) demonstrated a decrease in PSADT.			

ELISPOT Analysis of Anti-PSA T Lymphocytes Immune Responses – Since the primary arm of the immune response to tumor associated antigens has been documented as the T cell-mediated response, we examined the development of the responses over time after the initiation of vaccination. At each patient visit we obtained peripheral blood and isolated the lymphocytes by density gradient centrifugation. The majority of the lymphocytes were suspended in a cryopreservative solution and stored in liquid nitrogen for future analyses. At the end of the first 12 months following the initiation of therapy all of the samples for each patient will be thawed and an ELISPOT assay performed at one time. This is done to avoid inter-assay variability and will allow us to accurately compare the responses at each time point. When the lymphocyte yields were large such that we were able to cryopreserve sufficient numbers of cells for that single assay and have extra cells, we performed the ELISPOT assays on the freshly isolated cells. This is permitting us to obtain some preliminary measure of the anti-PSA T cells responses for the patients at the appropriate time points. However, the more definitive assays will be those performed on the stored cells after the 12 month time point. In the first year we did not do the 12 month assays, but report here the results of assays performed on patient samples when sufficient cells were available. Table 6 provides the data for those immune assays. For the patients in protocol #1, Arm A, 2/2 (100%) developed positive

anti-PSA T cell responses. For patients in protocol #1, Arm B, 2/2 (100%) developed positive anti-PSA T cell responses. For patients in protocol #2, 3/6 (50%) developed strong responses and 2/6 (33%) developed modest responses. For all patients in this protocol 5/6 (83%) developed positive anti-PSA T cells responses. For all patients in both protocols, 90% developed some level of anti-PSA T cell responses, with 70% developing strong responses.

Table 6
Ad/PSA Phase II Clinical Trial
ELISPOT Analysis of T Cell Responses

Patient	T Cell Frequency		Response
	Pre-Vaccination	Post-Vaccination	
APIIAHN-01	1/2X10E6	1/24,096	+
APIIAHN-02	1/33,000	1/12,000	+
APAADT-01	1/500,000	1/10,050	+
APAADT-02	1/46,512	1/7,463	+
APIIB-01	1/11,426	1/4,357	-
APIIB-02	1/1x10E8	1/10,870	+
APIIB-04	1/500,000	1/8,511	+
APIIB-05	1/130,000	1/2,850	+
APIIB-06	1/154,000	1/51,300	+/-
APIIB-07	1/133,000	1/64,500	+/-

REPORTABLE OUTCOMES:

Abstracts for presentation at the annual meetings of the American Association for Cancer Research (AACR) and the American Society for Clinical Oncology (ASCO) were submitted and accepted.

CONCLUSION:

Patients were enrolled in both protocols, vaccinated three times and followed by return visits to the University of Iowa Hospitals and Clinics and Iowa City VA Medical Center. No serious vaccine-related adverse events were reported for any of the patients. In the analysis of serum PSA and immune responses to PSA following the vaccinations, 67% of the patients demonstrated an increase in PSADT and 90% developed some level of anti-PSA T cell responses, with 70% developing strong responses.

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Vaena, D, Williams, RD, Joudi, F, Smith, M, Zehr, P, Eastman, J, Griffith, K, Madsen, T, Johnson, K, and Lubaroff, DM. A Phase II trial of an adenovirus/PSA vaccine for prostate cancer. Submitted to the American Association for Cancer Research.

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